IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Goddard et al. Serial No.: 09/964,994 Filed: September 26, 2001 Title: *NOVEL POLYPEPTIDES HAVING SEQUENCE SIMILARITY TO CYTOKINE RECEPTORS AND NUCLEIC ACIDS ENCODING THE SAME*	Group Art Unit: 1646 Examiner: KEMMERER, ELIZABETH Confirmation No: 2989 Customer No: 09157 **CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 2, 2003 P. Tobin Patty Tobin

DECLARATION OF THOMAS D. WU, M.D., Ph.D. UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Thomas D. Wu, M.D., Ph.D. do hereby declare and say as follows:

1. I am a Senior Scientist in the Department of Bioinformatics at Genentech, Inc., South San Francisco, California 94080.

2. From1999 to the present time, I have been the group leader for microarray informatics and analysis for the entire research department at Genentech. During this time, my responsibilities have included developing novel microarray algorithms for identifying genes with informative expression patterns and those with differential expression in subsets of tumors, for use in identifying targets useful in the therapy and diagnosis of cancer in humans. In addition, I have discovered several hundred cell surface markers specific for cancerous tumors in humans.

3. My scientific Curriculum Vitae, including my list of publications, is attached to and

forms part of this Declaration (Exhibit A).

4. I am familiar with a variety of techniques known in the art for detecting overexpression of genes in cancer, including microarray technology.

5. I understand the the above identified patent application describes experiments wherein cancerous tissues were screened for expression of PRO19598 (or its binding protein, PRO3301) by microarray technology. Specifically, expression was determined in cancerous tumor tissue(s) and in a "universal normal control". The "universal normal control" was made from pooled epithelial cells of various tissues, including liver, kidney and lung. The results of these studies showed that the gene encoding PRO3301 polypeptides was significantly overexpressed in specific tumor tissue(s) when compared to the "universal normal control".

6. I would like to verify that in addition to using the above described "universal normal control" in these microarray studies, parallel studies were concurrently conducted, wherein the level of expression of the PRO3301-encoding nucleic acid sequence was compared in both tumor samples and in control samples of the same tissue type as the tumor samples examined. These parallel studies compared the expression levels of PRO3301-encoding nucleic acid sequences in: (1) non-small cell lung adenocarcinoma versus normal lung tissue controls, (2) lung squamous cell carcinoma versus normal lung tissue controls, and (3) colorectal adenocarcinoma versus normal colorectal tissue controls. These contemporaneous studies demonstrated that compared to their normal healthy tissue counterparts, PRO3301-encoding nucleic acid sequences showed, on average, a 2.4 fold, 9.2 fold, and 5.3 fold increase in expression levels in non-small cell lung adenocarcinomas, lung squamous cell carcinomas, and colorectal adenocarcinomas, respectively. These results demonstrate that PRO3301-encoding nucleic acid sequences are significantly overexpressed in specific tumor tissue(s) when compared to their specific normal tissue controls and thus can be useful as a diagnostic marker for the presence or absence of such specific tumor(s) in a tissue sample of unknown pathology.

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

29 August 2003
Date

Thomas D. Wu, M.D., Ph.D.

Thomas D. Wu, M.D., Ph.D.

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EDUCATION

Stanford University Hospitals, Stanford, California
Internship and residency, Internal Medicine [Clinical Investigator Pathway], 1992–1994

Massachusetts Institute of Technology, Cambridge, Massachusetts
Ph.D., Computer Science, 1985–1992

George M. Sprowls Award for the most outstanding doctoral dissertation in the Department of Electrical Engineering & Computer Science

Dissertation: *A Decompositional Search Algorithm for Efficient Diagnosis of Multiple Disorders* (Committee: Ramesh Patil, Ph.D., Peter Szolovits, Ph.D., and Randall Davis, Ph.D.)

Harvard Medical School, Boston, Massachusetts
M.D. [Health Sciences and Technology curriculum], 1984–1992

Honors evaluations in all core clinical clerkships

Stanford University, Stanford, California
M.S., Electrical Engineering [Area: Statistical Signal Processing], 1983–1984
B.S. with Distinction and Honors, Electrical Engineering & Biological Sciences, 1980–1983

Frederick Emmons Terman Engineering Award for highest academic ranking (awarded to 7 students in Electrical Engineering)

Honors theses: *A Mathematical Model of the Multicalyceal Kidney* (Biological Sciences); *The Diffusion of Home Computers* (Values, Technology, & Society)

EXPERIENCE

Genentech, Inc., Department of Bioinformatics, South San Francisco, California
Senior Scientist, 2001–present
Scientist, 1999–2001

Group leader for microarray informatics and analysis for the entire research department. Supervise 5 employees who are responsible for imaging hardware, image analysis, database entry and annotation, software development, and data mining.

Designed a custom Affymetrix microarray containing all known and predicted transmembrane proteins, for use in identifying therapeutic targets.

Developed novel microarray algorithms for identifying genes with informative expression patterns and those with differential expression in subsets of tumors. Developed analytical tools for performing associative mining in large gene expression databases (BLIST).

Developed novel sequence analysis algorithms for identifying coding regions in cDNA sequences in the presence of sequence errors (ESTER) and for identifying transmembrane and signal peptides in protein sequences (TMDETECT).

Discovered several hundred cell surface markers specific for tumors. Discovered the majority of drug targets for the Tumor Antigen Project. Searched exhaustively for tissue-specific genes in the human genome, and characterized their biological properties.

Developed a genomic alignment program (SNAP) that is more accurate and faster than existing methods. Applied this program to map all available cDNA sequences to the human and mouse genomes.

Implemented graphical, interactive programs for viewing alignments between genomic and transcribed DNA (SEQVIEW) and for viewing and analyzing gene expression data (MAVIEW).

Stanford School of Medicine, Biochemistry Department (Adviser: Douglas Brutlag, Ph.D.)
Howard Hughes Medical Institute Physician Postdoctoral Fellow, 1996–1999
National Library of Medicine Postdoctoral Fellow, 1994–1996

Developed methods for detecting protein motifs with optimal accuracy, using regular expressions (EMOTIF) and scoring matrices (EMATRIX)

Developed techniques for performing superposition of multiple protein structures using regression techniques (MPOSE)

Developed a combinatorial algorithm for identifying regulatory elements in genomic sequences (PRISM)

Developed a segment-based dynamic programming algorithm for predicting gene structure (SEGUE) and explored statistical models for predicting alternative splice sites

FELLOWSHIPS AND HONORS

Physician Postdoctoral Fellowship, Howard Hughes Medical Institute, 1996–1999

One of 38 fellows selected among 283 applicants nationwide

National Library of Medicine Postdoctoral Fellowship, Stanford University Section on Medical Informatics, 1994–1996

Nominated for Chief Residency in Internal Medicine, Stanford Residency Training Program, 1993

George M. Sprowls Award, Massachusetts Institute of Technology, 1993

Most outstanding dissertation, Department of Electrical Engineering & Computer Science

Nominee, Distinguished Dissertation Award, Association for Computing Machinery, 1993

Sigma Xi, Massachusetts Institute of Technology, 1991

Martin Epstein Award, American Medical Informatics Association, 1990

First place, student paper competition, Symposium on Computer Applications in Medical Care

Medical Scientist Training Program Fellowship, Harvard Medical School, 1985–1992

Tau Beta Pi National Engineering Fellowship, 1983–1984

Phi Beta Kappa, Stanford University, 1983

Frederick Emmons Terman Engineering Award, Stanford University, 1983

Tau Beta Pi Laureate Award, 1983

One of three awards among all engineering undergraduates nationwide

Dean's Award for Service, Stanford University, 1983

One of two awards among all undergraduates for contributions to Stanford University and its students

Distinguished Service Award, Stanford School of Engineering, 1983

Tau Beta Pi, Stanford University, 1982

CERTIFICATIONS

Diplomate, American Board of Internal Medicine, 1995 (certificate 166357)

Examination scores in the 8th decile (core component) and 9th decile (non-core component)

Physician's and Surgeon's License, Medical Board of California, 1993 (license G77862)

TEACHING AND ADVISING EXPERIENCE

Biology 7200, Advanced Bioinformatics, California State University, Hayward, 2003. Guest lecture on Bioinformatics at Genentech.

Professional Development Series, Genentech Bioinformatics Department, 2000–present

Organized a weekly series of seminars for sharing knowledge and techniques within the department. Taught courses in graphical user interfaces, statistics, microarray data analysis, and client/server application programming.

Biochemistry 218, Computational Molecular Biology, Stanford University, 1996–1999. Five lectures on the topics of Profile Methods, Predicting Gene Structure, and Protein Motifs

Biology 227, Mathematical and Computational Molecular Biology, Stanford University, 1996. Lecture on Predicting Gene Structure.

Mentor, Asian-American Interactive Mentoring Program, Stanford University, 1995–1996

Adviser and Proctor, Board of Freshman Advisers, Harvard College, 1987–1992

Served as primary academic adviser and counselor in residence to 109 freshman over 5 years. Organized and led community and social activities in freshman dormitories.

PROFESSIONAL AND ACADEMIC SERVICE

Scientific Committee, Critical Assessment of Microarray Data Analysis, 2002–present

Steering Committee, Bay Area Bioinformatics Discussion Group, 2000–2002

Program Committee, International Conference on Intelligent Systems in Molecular Biology, 1998–1999

Committee on the Writing Requirement, Massachusetts Institute of Technology, 1986–1988

ADDITIONAL INFORMATION

Extensive experience in software development, including expertise in programming languages (C, C++, Perl, Lisp, Unix shell), multithreaded programming, socket interfaces, client/server programming, database programming (SQL, PL/SQL, Perl DBI, Oracle ProC, BerkeleyDB), statistical programming (Splus, R, PDL), graphical user interfaces (OpenGL, Tcl/Tk), and Web-based programming.

SOFTWARE LICENSES

Wu, T. D., Hastie, T., and Schmidler, S. C. Superposition and modeling of multiple protein structures. Docket 99–027, Stanford Office of Technology and Licensing.

Wu, T. D., Nevill-Manning, C. G., and Brutlag, D. L. Minimal-risk scoring matrices for characterizing protein families. Docket 98–130, Stanford Office of Technology and Licensing.

Nevill-Manning, C. G., Wu, T. D., and Brutlag, D. L. EMOTIF, IDENTIFY, and SCAN. Docket 97–083, Stanford Office of Technology and Licensing.

PATENTS

Compositions and methods for the diagnosis and treatment of tumor. U.S. patent applications 60/299500 (20 Jun 2001), 09/888257 (22 Jun 2001), 60/300880 (25 Jun 2001), 60/304813 (11 Jul 2001), 60/312312 (13 Aug 2001), 09/929769 (14 Aug 2001), 60/314280 (22 Aug 2001), 09/938418 (23 Aug 2001), 60/323268 (18 Sep 2001), 60/339227 (19 Oct 2001), 60/336827 (7 Nov 2001), 60/345444 (2 Jan 2002), 60/362004 (5 Mar 2002), 60/366869 (20 Mar 2002), 60/366284 (21 Mar 2002), 60/368679 (28 Mar 2002), 60/369724 (3 Apr 2002), 60/373160 (16 Apr 2002), 10/125166 (17 Apr 2002), 10/127966 (23 Apr 2002), 60/378885 (8 May 2002), 10/177488 (19 Jun 2002), 60/404809 (19 Aug 2002), 60/405645 (21 Aug 2002), 10/241220 (11 Sep 2002), 60/413192 (23 Sep 2002), 60/414971 (2 Oct 2002), 60/419008 (15 Oct 2002), 60/418988 (18 Oct 2002), 60/426847 (15 Nov 2002), 60/431250 (6 Dec 2002), 10/331496 (30 Dec 2002), 60/437344 (31 Dec 2002)

Compositions and methods for the treatment of immune related diseases. U.S. patent applications 60/394485 (8 Jul 2002), 60/410174 (11 Sep 2002), 60/425931 (12 Nov 2002)

Novel compositions and methods for the treatment of psoriasis. U.S. patent applications 60/410242 (11 Sep 2002), 60/414006 (25 Sep 2002)

Compositions and methods for treating immune disorders. U.S. patent applications 60/411392 (16 Sep 2002), 60/414484 (26 Sep 2002), 60/422472 (29 Oct 2002), 60/423394 (1 Nov 2002)

Methods of treating renal cell carcinoma. U.S. patent applications 60/344534 (18 Oct 2001), 10/271690 (16 Oct 2002)

Compositions and methods for the treatment of natural killer cell related diseases. U.S. patent application 60/425235 (8 Nov 2002)

RECENT INVITED TALKS

Tissue-specific genes in the human and mouse genomes. American Society of Biochemistry and Molecular Biology Annual Meeting, San Diego, CA, 13 April 2003.

Tumor-specific and tissue-specific genes in the human genome. Keystone Symposium on Functional Genomics: Global Analysis of Complex Biological Systems, Santa Fe, NM, 24 February 2003.

Computational studies of the genome and transcriptome: Applications to cancer genetics and cancer therapeutics, Stanford Medical Informatics, Stanford, CA, 6 December 2002.

Analysing DNA microarray data for cancer research. National Cancer Research Institute Symposium on Meeting the Challenges of Today's Molecular Pathology, organized by the National Translational Cancer Research Network, London, 18 June 2002.

Analyzing gene expression data from DNA microarrays. IEEE Bioinformatics Conference, Stanford, CA, 11 May 2002.

Analyzing gene expression data to identify candidate genes. Bay Area Bioinformatics group, Stanford, CA, 23 August 2001.

Finding candidate genes for drug discovery. Beyond the Genome conference, organized by the Cambridge Healthtech Institute, San Francisco, CA, 17 June 2001.

Recognizing and discovering patterns in genomic data. Department of Bioengineering, University of California, Berkeley, CA, 14 June 1999.

Recognizing and discovering patterns in genomic data. College of Health Sciences and Technology, M.I.T., Cambridge, MA, 26 April 1999.

Recognizing and discovering patterns in genomic data. Lawrence Berkeley National Laboratory, Berkeley, CA, 2 March 1999.

Superposition and modeling of multiple protein structures. Department of Medical Information Sciences, University of California, San Francisco, CA, 13 May 1998.

PEER-REVIEWED PUBLICATIONS

Wu, T. D. and Watanabe, C. K. SNAP: A spliced nucleotide alignment program. Submitted to Nucleic Acids Research.

Zhou, Y., Zhang, Y., Luoh, S-M., Watanabe, C., Wu, T. D., Ostland, M., Wood, W. I., and Zhang, Z. Genome-wide identification of chromosomal regions of increased tumor expression by transcriptome analysis. Cancer Research, in press.

Smith, V., Shen, E. F., Wieand, D., Landon, T. H., Wong, N. A. C. S., Lessells, A. M., Paterson-Brown, S., Tang, J. Z., Wu, T. D., Hillan, K. J., and Penman, I. D. Expression analysis of the metaplasia–dysplasia–carcinoma sequence in Barrett's esophagus and adenocarcinoma. Submitted to Nature Medicine.

Wu, T. D., Schiffer, C. A., Gonzales, M. J., Taylor, J., Kantor, R., Chou, S., Israelski, D., Zolopa, A. R., Fessel, J., and Shafer, R. W. Mutation patterns and structural correlates in HIV-1 protease following varying degrees of protease inhibitor treatment. Journal of Virology 77, 2003, 4836–4847.

Gonzales, M. J., Wu, T. D., Taylor, J., Belitskaya, I., Kantor, R., Israelski, D., Chou, S., Zolopa, A. R., Fessel, W. J., and Shafer, R. W. Extended spectrum of HIV-1 reverse transcriptase mutations in patients receiving multiple nucleoside analog inhibitors. AIDS 17, 2003, 791–799.

Gerritsen, M. E., Soriano, R., Yang, S., Ingle, G., Zlot, C., Toy, K., Winer, J., Draksharapu, A., Peale, F., Wu, T. D., and Williams, P. M. The use of in silico data filtering to identify potential angiogenic targets from a large in vitro gene profile data set. Physiological Genomics 10, 2002, 13–20.

Gerritsen, M. E., Peale, F. V., and Wu, T. Gene expression profiling in silico: Relative expression of candidate angiogenesis associated genes in renal cell carcinomas. Experimental Nephrology 10, 2002, 114–119.

Wu, T. D. Large-scale analysis of gene expression profiles. Briefings in Bioinformatics 3, 2002, 7–17.

Wu, T. D. Analysing gene expression data from DNA microarrays to identify candidate genes. Journal of Pathology 195, 2001, 53–65.

Wu. T. D., Nevill-Manning C. G., and Brutlag, D. L. Fast probabilistic analysis of sequence function using scoring matrices. Bioinformatics 16, 2000, 233–244.

Wu, T. D., Nevill-Manning, C. G., and Brutlag, D. L. Minimal-risk scoring matrices for sequence analysis. Journal of Computational Biology 6, 1999, 219–235.

Wu, T. D., Schmidler, S. C., Hastie, T., and Brutlag, D. L. Regression analysis of multiple protein structures. Journal of Computational Biology 5, 1998, 585–595.

Chin, R. L., Sporer, K. A., Cullison, B., Dyer, J. E., and Wu, T. D. Clinical course of gamma-hydroxybutyrate ingestion. Annals of Emergency Medicine 31, 1998, 716–722.

Wu, T. D., Schmidler, S. C., Hastie, T., and Brutlag, D. L. Regression analysis of multiple protein structures. Proceedings, Second Annual International Conference on Computational Molecular Biology, ACM Press, 1998, 276–284.

Nevill-Manning, C. G., Wu, T. D., and Brutlag, D. L. Highly specific protein sequence motifs for genome analysis. Proceedings of the National Academy of Sciences 95, 1998, 5865–5871.

Wu, T. D., Schmidler, S.C., Hastie, T., and Brutlag, D. L. Superposition and modeling of multiple protein structures using affine transformations: Analysis of the globins. Proceedings, Pacific Symposium on Biocomputing, World Scientific Publishing, 1998, 509–520.

Nevill-Manning, C. G., Sethi, K., Wu, T. D., and Brutlag, D. L. Enumerating and ranking discrete motifs. Proceedings, Fifth International Conference on Intelligent Systems in Molecular Biology, AAAI Press, 1997, 202–209.

Wu, T. D., A segment-based dynamic programming algorithm for predicting gene structure. Journal of Computational Biology 3, 1996, 375–394.

Wu, T. D., and Brutlag, D. L. Discovering empirically conserved amino acid substitution groups in databases of protein families. Proceedings, Fourth International Conference on Intelligent Systems in Molecular Biology, AAAI Press, 1996, 230–240.

Wu, T. D., and Brutlag, D. L. Identification of protein motifs using conserved amino acid properties and partitioning techniques. Proceedings, Third International Conference on Intelligent Systems in Molecular Biology, AAAI Press, 1995, 402–410.

Wu, T. D. A problem decomposition method for efficient diagnosis and interpretation of multiple disorders. Computer Methods and Programs in Biomedicine 35, 1991, 239–250.

Wu, T. D. Probabilistic evaluation of candidate sets for multidisorder diagnosis. In P. P. Bonissone, M. Henrion, L. N. Kanal, and J. Lemmer, editors, Uncertainty in Artificial Intelligence, Elsevier Press, Amsterdam, 1991, 107–115.

Wu, T. D. Domain structure and the complexity of diagnostic problem solving. Proceedings, Ninth National Conference on Artificial Intelligence, AAAI Press, 1991, 855–861.

Wu, T. D. Probabilistic evaluation of candidate sets for multidisorder diagnosis. Proceedings, Sixth Conference on Uncertainty in Artificial Intelligence, 1990, 460–467.

Wu, T. D. A problem decomposition method for efficient diagnosis and interpretation of multiple disorders. Proceedings, Fourteenth Symposium on Computer Applications in Medical Care, IEEE Press, 1990, 357–364.

Wu, T. D. Efficient diagnosis of multiple disorders based on a symptom clustering approach. Proceedings, Eighth National Conference on Artificial Intelligence, AAAI Press, 1990, 357–364.

Wu, T. D. Symptom clustering and syndromic knowledge in diagnostic problem solving. Proceedings, Thirteenth Symposium on Computer Applications in Medical Care, IEEE Press, 1989, 45–49.